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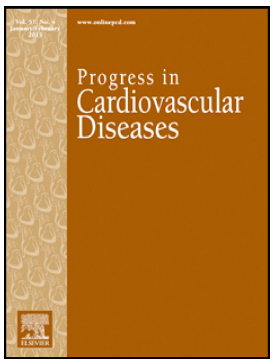

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PII: S0033-0620(17)30165-2
DOI: https://doi.org/10.1016/j.pcad.2017.12.003
Reference: YPCAD 854

To appear in:

Received date: 17 December 2017
Accepted date: 17 December 2017

Please cite this article as: Abhishek Sharma, Aakash Garg, Sammy Elmariah, Douglas Drachman, Chukwudi Obiagwu, Ajay Vallakati, Samin K. Sharma, Carl J. Lavie, Debabrata Mukherjee, Ron Waksman, Giulio G. Stefanini, Fausto Feres, Jonathan D. Marmur, Gérard Helft , Duration of Dual Antiplatelet Therapy Following Drug-Eluting Stent Implantation in Diabetic and Non-Diabetic Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Ypcad(2017), https://doi.org/10.1016/j.pcad.2017.12.003

Duration of Dual Antiplatelet Therapy Following Drug-Eluting Stent Implantation in Diabetic and Non-Diabetic Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Short title: DAPT after DES in Diabetic and Non-Diabetic Patients

Disclosure: None

ABSTRACT:

Background: Diabetic patients account for an increasing number of patients undergoing percutaneous coronary intervention (PCI). However, diabetes mellitus (DM) is associated with increased residual platelet activity during dual antiplatelet treatment (DAPT) and DM patients have worse clinical outcomes after PCI as compared to non-DM.

Objective: To evaluate efficacy and safety of short duration DAPT (S-DAPT) and long duration DAPT (L-DAPT) after drug eluting stent (DES) implantation in DM and non-DM patients.

Methods: We searched Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) to identify randomized controlled trials (RCTs) assessing the effect of S-DAPT versus L-DAPT after DES implantation in DM and non-DM patients. Efficacy endpoints were all-cause mortality, cardiac mortality, myocardial infarction (MI), stent thrombosis (ST), target vessel revascularization (TVR), and composite end point of net adverse clinical events (NACE) (all cause mortality, cardiac mortality, MI, ST, TVR, stroke, major bleeding). Safety endpoints were major bleeding and stroke. Event rates were compared using a forest plot of relative risk using a random effects model.

Results: We included eight RCTs that randomized 28,318 patients to S-DAPT versus L-DAPT (8,234 DM and 20,084 non-DM). S-DAPT was associated with an increased rate of ST in non-DM patients [3.67 (2.04, 6.59)]. There was no significant difference in the rate of all cause mortality, cardiac mortality, ST, MI, TVR, major bleeding, stroke and NACE with S-DAPT and L-DAPT in DM patients [1.19 (0.72-1.95); 1.25 (0.69, 2.25);

1.52 (0.70, 3.29); 1.33 (0.88, 2.01); 1.39 (0.89, 2.17); 0.92 (0.19, 4.42); 0.98 (0.29, 3.28); and 0.94 (0.57, 1.54) respectively]. Further, there was no significant difference in the rate of all cause mortality, cardiac mortality, MI, TVR, major bleeding, stroke and NACE with S-DAPT and L-DAPT in non-DM patients [0.93 (0.58, 1.48); 0.75 (0.42, 1.35); 1.52 (0.81, 2.83); 0.99 (0.71, 1.39); 0.72 (0.28, 1.84); 1.01 (0.40, 2.56); and 1.01 (0.77, 1.32) respectively].

Conclusion: Compared to L-DAPT, S-DAPT was associated with significant increase in rate of ST in non-DM patients. Duration of DAPT had no significant impact on rates of all cause mortality, cardiac mortality, MI, ST and TVR among DM patients.

Key Words: Dual anti-platelet therapy, Drug eluting stents, Diabetes

ABBREVIATIONS

CAD: Coronary Artery Disease

DAPT: Dual Anti-platelet Therapy

DES: Drug Eluting Stent

DM: Diabetes Mellitus

L-DAPT: Long Dual Anti-platelet Therapy

MI: Myocardial Infarction

NACE: Net Adverse Cardiovascular Event

PCI: Percutaneous Coronary Intervention

RCT: Randomized Controlled Trial

S-DAPT: Short Dual Anti-platelet Therapy

ST: Stent Thrombosis

TVR: Target Vessel Revascularization

INTRODUCTION:

The prevalence of diabetes mellitus (DM) is increasing globally, and optimal care of DM patients remains a challenge for health care providers. Patients with DM have higher prevalence of coronary artery disease (CAD) and account for an increasing number of patients undergoing percutaneous coronary intervention (PCI) [1]. However, DM patients have worse clinical outcomes after PCI as compared to non-DM [1, 2].

Dual antiplatelet therapy (DAPT) using a combination of aspirin and a P2Y12 inhibitor is used for the prevention of ischemic complications after PCI. However, the optimal duration of DAPT after drug-eluting stent(s) (DES) implantation remains unclear [3]. Several studies have reported an increase in bleeding complications with longer duration (>12 months) of DAPT (L-DAPT) compared to short duration (</=12 months) DAPT (S-DAPT), without any significant improvement in the rates of atherothrombotic complications [4-10]. However, the large multicenter DAPT Study recently demonstrated improved clinical outcomes with longer duration of DAPT (L-DAPT) compared to short duration DAPT (S-DAPT) [11]. Pooled analyses of various randomized controlled trials (RCTs) have reported conflicting results [12-20]. Inconsistent results are likely due to the evaluation of different studies and patient subgroups. Diabetes mellitus is associated with a prothrombotic state secondary to endothelial dysfunction, hyper-coagulability, and platelet activation. Thus, the benefits of L-DAPT versus S-DAPT in diabetic patients warrant investigation. Against this background, we performed a meta-analysis of RCTs to

evaluate the efficacy and safety of S-DAPT and L-DAPT after DES implantation in DM and non-DM patients.

METHODS:

We followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses of RCTs for the protocol of our meta-analysis [21].

We systematically searched PubMed, CINAHL, Cochran CENTRAL, Embase, Scopus and Web of Science databases for randomized clinical trials comparing different durations of DAPT after DES implantation in patients with and without DM. Pertinent trials were also searched in clinicaltrials.gov and in the proceedings of major international cardiology meetings (ACC, AHA, ESC, The Society for Cardiac Angiography and Interventions). In addition, the reference lists of the identified studies were searched for any potential relevant studies. DAPT was defined as aspirin plus a P2Y12 receptor inhibitor, after coronary DES implantation. S-DAPT and L-DAPT were defined as duration of DAPT after DES implantation </=12months and >12months respectively. All relevant combinations of following keywords "aspirin", "P2Y12 receptor inhibitor ", "clopidogrel", "Plavix", "prasugrel", "Effient", "ticagrelor", "Brilinta", "thienopyridine", "dual antiplatelet therapy", "DAPT", "drug eluting stents", "DES", "diabetes mellitus", "DM", "non diabetics", "non DM", "death", "mortality", "survival", "cardiac mortality", "stent thrombosis", "Global Utilization Of Streptokinase

And Tpa For Occluded Arteries (GUSTO) bleeding", stroke, myocardial infarction, "randomized controlled trial", "random", "random allocation", "double-blind", and "single-blind" were included for database search. We manually searched references of identified studies. Only studies published between January 1, 2002 to June 30, 2016 were included. No language restrictions were applied. Studies, which did not report the absolute numbers of events in DM and non-DM patients after DES implantation, were excluded from the analysis. The corresponding authors of the relevant studies were queried for required quantitative details not in the published manuscripts.

Two reviewers (AS, AG) independently screened the titles and abstracts for relevance. The full texts of selected manuscripts were reviewed for inclusion or exclusion using the above mentioned selection criteria. Two reviewers (AS, AG) independently determined the articles to be included and excluded, and data from the relevant articles were extracted using pre-defined extraction forms. Any disagreements in data extraction were discussed until consensus was reached. Baseline patient characteristics and follow up data was extracted from selected studies at the end of follow up period: all-cause mortality, cardiac mortality, myocardial infarction (MI), stent thrombosis (ST), target vessel revascularization (TVR), major bleeding, stroke and net adverse cardiovascular event (NACE), the composite of all cause mortality, cardiac mortality, MI, ST, TVR, stroke, major bleeding. MI and major bleeding was defined per trial definition. ST was defined as per Academic Research Consortium (ARC) [22].

The statistical analysis was performed according to the recommendations from the Cochrane Collaboration using Review Manager Version 5.1 (The Nordic Cochrane Center, The Cochrane Collaboration, 2008, Copenhagen). A random-effects model with inverse variance weighting was used to calculate odds ratio (OR) and 95% confidence interval, associated with S-DAPT versus L-DAPT for above end points. Forest plots were used to observe the overall effect of studies for each endpoint. Heterogeneity between studies was assessed using Cochrane's Q test and I^2 statistic, which denotes the percentage of total variation across studies that is a result of heterogeneity rather than chance. $I^2 < 25$ % was considered as low heterogeneity and $I^2 > 75$ % as high. Heterogeneity was considered significant if the p value was less than 0.05. Publication bias was assessed by Begg's test and Egger's regression test.

RESULTS:

2819 publications were found at initial search and after abstract and manuscript evaluation eight studies are selected for final analysis (Figure 1). Investigators of OPTIMIZE and OPTIDUAL trials have shared their data on outcomes for DM and non-DM patients after PCI for this analysis, which was not reported/published before [5, 8]. In the selected eight RCTs, 28,318 patients were randomized to S-DAPT (N=14,095) versus L-DAPT (14, 203) (Table 1) [4-11]. Out of 28,318 patients 8,234 had DM and 20,084 were non-diabetics. Median follow up period in studies included in our analysis varied from 9 months to 33 months with overall median follow up of 12 months after

completion of L-DAPT. Use of second generation DES varied from 36% to 100%. Baseline characteristics of patients and studies included in the final analysis are summarized in Table 2.

On analysis, of 18025 patients (5417 DM and 12608 non-DM), S-DAPT was associated with an increased rate of ST in non-DM patients [3.67 (2.04, 6.59), p<0.0001] (Figure2). There was no significant difference in the rate of ST with S-DAPT among DM patients [1.52 (0.70, 3.29), p=0.29] (Figure2) (Table 3). There was borderline interaction between subgroups for ST ($P_{interaction}$=0.07). Overall, regardless of DAPT duration, DM patients have higher rates of ST (0.72%) than non-DM patients (0. 57%). There was also no significant difference in the rate of MI with S-DAPT and L-DAPT in DM [1.33 (0.88, 2.01), p=0.18] and non-DM [1.52 (0.81, 2.83), p=0.19] patients on analysis of 18025 patients (5417 DM and 12608 non-DM) (Figure 3) (Table 3). DM patients have higher rates of MI (3.30%) than non-DM (2.08%) irrespective of the duration of DAPT.

There was also no significant difference in the rate of all cause mortality, and cardiac mortality with S-DAPT and L-DAPT in DM [1.19 (0.72-1.95) and 1.25 (0.69, 2.25) respectively] and non-DM-patients [0.93 (0.58, 1.48); and 0.75 (0.42, 1.35) respectively] (Figure 4, 5) (Table 3). However, overall event rates of both all-cause mortality (3.16% vs 1.89%), and cardiac mortality (2.01% vs 0.83%) were higher for DM patients as compared to non-DM patients.

Similarly, no significant difference was found between S-DAPT and L-DAPT for TVR, major bleeding and stroke for DM [1.39 (0.89, 2.17); 0.92 (0.19, 4.42); and 0.98 (0.29, 3.28) respectively] and non-DM patients [0.99 (0.71, 1.39); 0.72 (0.28, 1.84); and 1.01 (0.40, 2.56) respectively] (Supplementary Figure 1, 2, 3) (Table 3). On analysis of 16,980 patients (4762 with DM and 12218 non-DM patients) there was no significant difference in the rate of composite end point-NACE with S-DAPT and L-DAPT for DM [0.94 (0.57, 1.54)] and non-DM patients [1.01 (0.77, 1.32)] (Supplementary figure 4). However, overall event rates were higher among DM patients compared to non-DM (4.49% vs 3.01%).

DISCUSSION:

In our meta-analysis of RCTs in which patients were analyzed according to DM status, S-DAPT compared to L-DAPT was associated with a significant increase in rate of ST in non-DM patients. However, there was no significant difference in the rate of all cause mortality, cardiac mortality, MI, ST and TVR with S-DAPT among DM patients.

Although widespread use of DES has improved overall clinical outcomes [23, 24], sustained risk of ST and MI remain a major concern in DM patients [25-27]. This elevated risk has been partly attributed to existence of a pro-thrombotic state in DM patients secondary to several factors, including endothelial dysfunction, hyper-coagulation and platelet hyperactivation [28, 29]. Furthermore, patients with impaired glucose metabolism have been reported to have a suboptimal biochemical response to

aspirin (a mainstay agent for DAPT)—'aspirin resistance' [30, 31]. Possible causes of this suboptimal response have been proposed including aspirin formulation used and dose of aspirin given [32]. Recently, in a randomized, single-blind, triple-crossover study Bhatt et al, investigated if suboptimal response to aspirin in diabetic patients is mediated via decrease oral bioavailability [33]. Forty patients with type 2 DM and without cardiovascular disease were randomized to receive a plain aspirin tablet, a PL2200 aspirin capsule (modified-release lipid-based aspirin), and a delayed-release enteric-coated (EC) aspirin caplet. There was no significant difference in aspirin response between plain aspirin and PL2200 aspirin ($p=0.41$), whereas aspirin response was quicker with the former two when compared to EC aspirin ($p<0.001$). The patients on EC aspirin were found to have lower levels of plasma aspirin, secondary to decreased absorption. Therefore, use of non-EC aspirin formulation might be more appropriate in this patient population.

DAPT has been shown to be protective against early and late ischemic events after DES implantation, although the optimal duration remains unclear [12-20]. Even though DM patients have higher prevalence of CAD and they undergo coronary revascularization procedures, including PCI, more often than non-DM patients, there is paucity of data evaluating the impact of DM on duration of DAPT [34]. DM has been considered an independent variable in DAPT score, presence of which might favor L-DAPT after PCI [35]. However, in recent patient-level pooled analysis of 11,473 patients, Gargiulo and colleagues have reported that L-DAPT was associated with increased bleeding

complications in both DM and non-DM patients, without significant reduction in ischemic events [36].

In this context, our meta-analysis of RCTs provides important insights into relationship of DAPT duration with clinical outcomes among DM and non-DM patients after implantation of DES. Our results suggest that DM patients have higher rate of adverse CV events than non-DM patients after PCI with DES implantation irrespective of DAPT duration. Further, L-DAPT compared to S-DAPT might not be effective in reducing adverse cardiovascular outcomes after PCI in DM patients.

While placing our results in the context of above findings, several points are worth mentioning. First, accelerated neointimal hyperplasia leading to endothelialization may account for the differential effect of prolonged DAPT on ST in patients with DM [37, 38]. Second, diminished impact of antiplatelet agents in DM, especially clopidogrel, on platelet inhibition may explain a higher incidence of ST in the first 6 months, as seen in S-DAPT arm of EXCELLENT trial, where the reported ST events occurred while the patients were still on DAPT [7, 39]. Third, platelet hyper-reactivity has been implicated as a cause of increased thrombogenesis in DM, suggesting a place for more potent anti-platelets [40, 41]. Although, relatively low number of events and inclusion of studies with short-term follow up [7, 10] precludes definitive conclusions, our results suggest complex interaction of various clinical end points and DM after DES implantation.

DM has been shown to be an independent risk factor for ST [42]. One of the major issues surrounding DAPT duration is a sustained risk of late (1-12 months) [43] and very late (>12 months) ST [44] after DES implantation. Several medium-sized RCTs have shown that S- DAPT is non-inferior to L- DAPT in terms of incidence of ST [5, 6, 10], however these studies did not possess sufficient statistical power to assess ST. The Dual Antiplatelet Therapy (DAPT) study, the only study adequately powered for assessing DAPT duration on rates of ST, randomized event-free patients at 12 months to placebo versus extended (30 months) duration of DAPT and found a significantly reduced risk of ST with the L-DAPT (0.4% vs 1.4%, p <0.001) [22]. However, consistent with our finding, the protective effect of L-DAPT in DAPT trial was attenuated in DM patients (0.6% vs 1.1%), compared to non -DM (0.3% vs 1.5%) [11]. Similarly, in analysis of the diabetic subgroup of the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) trial, there was trend toward increased risk of ST with S-DAPT when compared with standard 12-month DAPT [7]. Our analysis demonstrated significantly increased risk of ST with S-DAPT relative to L-DAPT in non-diabetic patients. Although in DM patients there was no statistically significant difference in the rate of ST with L-DAPT as compared to S-DAPT. This could be partly due to relatively small number of patients and events in the DM arm (5417 patients and 39 ST) compared to non-DM (12608 patients and 72 ST). This could be due to higher baseline platelet activity in DM patients, which remains higher than non-DM even after DAPT.

Our analysis has several limitations. First, this is a meta-analysis performed on study-level data due to non-availability of patient-level data. Thus, covariate-adjusted analyses

for possible confounders like generation of DES, clinical presentation/indication of PCI, location and complexity of lesions during PCI, baseline clinical characteristics (e.g. insulin dependent or non-insulin dependent DM, renal dysfunction, heart failure) could not be performed. Similarly, due to lack of patient-level information regarding use of statins, beta-blockers or renin–angiotensin system blockers, we could not evaluate their impact on the relative efficacy of prolonged DAPT in DM and non-DM patients. Studies included in our meta-analysis randomized patients with various clinical presentations and characteristics, thus it is unlikely that these variables would have confounded our results due to selection bias; however, this cannot be completely excluded on the basis of current analysis. Second, prasugrel and ticagrelor have been shown to be associated with decrease in the rate of ST compared to clopidogrel and have recently been recommended by the American College of Cardiology/American Heart Association and European Society of Cardiology for management of ACS [45, 46]. In the present study, we were unable to evaluate duration of DAPT with prasugrel and ticagrelor, as studies included in our analysis did not compare duration of DAPT using these antiplatelets separately. However, such variations in DAPT reflect real world clinical practice, where different second antiplatelet agents are selected based on operator choices, clinical settings and drug availability. Third, trials included in our analysis were open label and timing of randomization was not the same in all studies, which could dilute the difference between the S-DAPT and L-DAPT arms, especially if ischemic or bleeding events have occurred before randomization or DAPT discontinuation.

CONCLUSIONS:

Compared to L-DAPT, S-DAPT was associated with significant increase in rate of ST in non-DM patients. Duration of DAPT had no significant impact on rates of all cause mortality, cardiac mortality, MI, ST and TVR among DM patients.

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FIGURES LEGENDS:

Figure 1 The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart for the trial selection process

Figure 2: Forest plot for stent thrombosis for DM and non-DM patients

Figure 3: Forest plot for myocardial infarction for DM and non-DM patients

Figure 4. Forest plot for all cause mortality for DM and non-DM patients

Figure 5. Forest plot for cardiac mortality for DM and non-DM patients

Tables:

STUDY	DESIGN	Time to Randomization	Inclusion Criteria	Exclusion Criteria	Primary end-point
RESET (2012)	Randomized, open label, multicentre	At index PCI	20-85 years old; ≥50% stenosis; elective PCI; stable angina, unstable angina, or acute MI	CI to anti-platelets; STEMI within 48 h; CVA; PAD; thromboembolism; ST; ISR; CTO; LM stenosis>50%; History of DES Implantation; cardiogenic shock.	Composite of Cardiac Death, MI, ST, ischemia-driven TVR or Bleeding at 12 Months after PCI
OPTIMIZE (2014)	Randomized, open label, multicentre	At index PCI	Stable angina or silent ischemia or low risk ACS as defined by unstable angina or recent (but not acute) myocardial infarction (<30 days)	STEMI for Primary or Rescue PCI; BMS less than 6 months prior to index procedure; previous treatment with DES; scheduled surgery within 12 months; CI to anti-platelets; ISRs	Composite of Death, MI, Stroke or Major Bleeding at 12 Months after PCI
ISAR-SAFE (2014)	Randomized, double-blind,	6 months after Index PCI	Patients on clopidogrel at 6	Previous ST; DES in LM; MI in the previous 6 months; Planned major	Composite of Death, MI, Stroke or ST or TIMI major

	multicentre		(−1/+2) months after PCI with DES	surgery within next 6 months; CI to anti-platelets; OAC; Prior ICH	Bleeding at 15 Months after PCI
EXCELLENT (2012)	Randomized, open label, multicentre	At index PCI	≥1 lesion native coronary vessel; >50% stenosis; stable angina, unstable angina, recent MI, silent ischemia, positive functional study, or reversible changes on ECG consistent with ischemia	MI within 72 hours; any prior stent implanted in the target vessel; cardiogenic shock; major bleeding within 3 months; elective surgical procedure within 12 months; left main stenosis > 50%; CTOs; bifurcation lesions requiring 2-stent strategy.	Composite of Cardiac Death, MI or TVR at 12 Months after PCI
OPTIDUAL (2015)	Randomized, open label, multicentre	12 months after index PCI	Stable angina, silent ischaemia, or acute coronary syndrome with ≥1 lesion	Requirement for oral anticoagulation, DES implantation in an unprotected left main coronary artery, and	Composite of all-cause mortality, non-fatal myocardial infarction, stroke, or major bleeding.

			with stenosis >50% located in a native vessel implanted with ≥1 DES of any type.	malignancies or other coexisting conditions associated with a life expectancy of <2 years	
ARCTIC (2014)	Randomized, open label, multicentre	12 months after index PCI	≥18 years and eligible for PCI with planned use of ≥1 DES.	Primary PCI for STEMI; chronic anticoagulation or bleeding diathesis; CI to APT; active bleeding or major surgery within 3 months; scheduled surgery within 1 year	Composite of Death, MI, Stroke or TIA, urgent revascularization or ST
DES-LATE (2014)	Randomized, open label, multicentre	12 months after index PCI	DES within 12 months; on DAPT; no MACE (MI, stroke, repeat PCI) or major bleeding since PCI.	CI to antiplatelet drugs, concomitant vascular disease or recent ACS requiring clopidogrel use	Composite of Cardiac Death, MI or Stroke at 24 Months after PCI
DAPT	Randomiz	12 months	>18	Planned major surgery within	ST; Composite of

(2014)	ed, double-blind, multicentre	after index PCI	years undergoing FDA-approved PCI with DES or BMS; No MACE or bleeding within 12 months after procedure.	the 30 months post enrollment; OAC; Both BMS and DES during index procedure; PCI or surgery between 6 weeks post-PCI and randomization	death, MI, stroke; and Moderate or severe GUSTO bleeding

Table 1. Baseline characteristics of studies included in analysis

ACS: Acute coronary syndrome, BMS: bare metal stent, CI: contraindication; CKD: Chronic kidney disease, CTO: Chronic total occlusion, ECG: Electrocardiogram, FDA: Food and Drug Administration, LM: Left main, TVR: target vessel revascularization, STEMI: ST segment elevation myocardial infarction, NSTEMI: non ST segment elevation myocardial infarction, PCI: Percutaneous coronary interventions, MI: myocardial infarction, DES, drug eluting stents, OAC: oral anticoagulant, MACE: major adverse cardiac event, GUSTO: Global Utilization Of Streptokinase And Tpa For Occluded Arteries, SVG: Saphenous venous grafts, UPLMA: Unprotected left main artery.

ARCTIC: Assessment by a double Randomisation of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and, of Treatment Interruption versus Continuation 1 year after stenting; DAPT: The dual antiplatelet therapy study; DES-LATE: the Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event; EXCELLENT: Efficacy of Xience/Promus Versus Cypher in rEducing Late Loss After stENTing; ISAR-SAFE: Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; OPTIDUAL: Optimal Duration of Dual Antiplatelet Therapy After Drug-eluting Stent Implantation; OPTIMIZE: Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; RESET: REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation).

Study	N Total	N DM	N Non-DM	Follow-up (months)	Age (y)	Male (%)	HTN (%)	HLD (%)	Prior MI (%)	ACS (%)	2nd gen stent (%)
RESET	2117	3 months= 146 12 months= 146	3 months = 913 12 months = 912	12	62	64	62	59	2	28	85
OPTIMIZE	3119	3 months= 554 12 months= 549	3 months = 1009 12months= 1007	12	62	63	87	64	35	32	100
ISAR-SAFE	3997	6 months= 495 12 months= 484	6 months = 1501 12 months = 1517	9	67	81	90	87	25	40	89
EXCELLENT	1443	6 months= 272	6 months = 450	12	63	65	73	76	5	51	75

		12 months= 278	12months= 443								
ARCTIC	1259	12 months= 222 18 months= 198	12 months= 402 18 months= 437	17	64	80	60	67	30	26	63
DES-LATE	5045	12 months= 709 30 months= 709	12 months= 1805 30 months= 1822	24	62	69	57	NA	4	61	36
DAPT	9961	12 months= 1481 30 months= 1556	12 months= 3460 30 months= 3464	18	62	75	75	NA	22	26	61
OPTIDUAL	1385	12 months= 222	12 months= 468 48	33	64	81	59	NA	17	36	66

	48 months= 213	months = 482

Table 2. Baseline patient characteristics in the studies included in the analysis

%: percent; ACS: Acute coronary syndrome, N: Number of patients, DM: diabetes mellitus, MI: myocardial infarction, HTN: hypertension, HLD: hyperlipidemia

ARCTIC: Assessment by a double Randomisation of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and, of Treatment Interruption versus Continuation 1 year after stenting; DAPT: The dual antiplatelet therapy study; DES-LATE: the Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event; EXCELLENT: Efficacy of Xience/Promus Versus Cypher in rEducing Late Loss After stENTing; ISAR-SAFE: Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; OPTIDUAL: Optimal Duration of Dual Antiplatelet Therapy After Drug-eluting Stent Implantation; OPTIMIZE: Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; RESET: REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation).

	All patients (N=28,318)	Diabetics (N=8,234)	Non-Diabetics (N=20,084)	$P_{interaction}$	Hetero-geneity (I^2)
All cause mortality	1.04 [0.74, 1.46]	1.19 [0.72-1.95]	0.93 [0.58, 1.48]	0.48	0%
Cardiac mortality	0.97 [0.64, 1.46]	1.25 [0.69, 2.25]	0.75 [0.42, 1.35]	0.23	0%
MI	1.48 [1.00, 2.19]	1.33 [0.88, 2.01]	1.52 [0.81, 2.83]	0.73	58%
ST	2.16 [1.21, 3.85]	1.52 [0.70, 3.29]	3.67 [2.04, 6.59]	0.07	21%
TVR	1.12 [0.85, 1.47]	1.39 [0.89, 2.17]	0.99 [0.71, 1.39]	0.24	20%
Major bleeding*	0.77 [0.34, 1.72]	0.92 [0.19, 4.42]	0.72 [0.28, 1.84]	0.79	0%
Stroke	1.00 [0.48, 2.09]	0.98[0.29, 3.28]	1.01 [0.40, 2.56]	0.98	0%
NACE	0.97 [0.76, 1.25]	0.94 [0.57, 1.54]	1.01 [0.77, 1.32]	0.81	48%

S-DAPT compared with L-DAPT in diabetics and non-diabetics; *: GUSTO or TIMI major bleeding

MI: myocardial infarction; NACE: net adverse clinical events; ST: Stent thrombosis (definite or probable); TVR: target vessel revascularization

Conflict of interest: None.

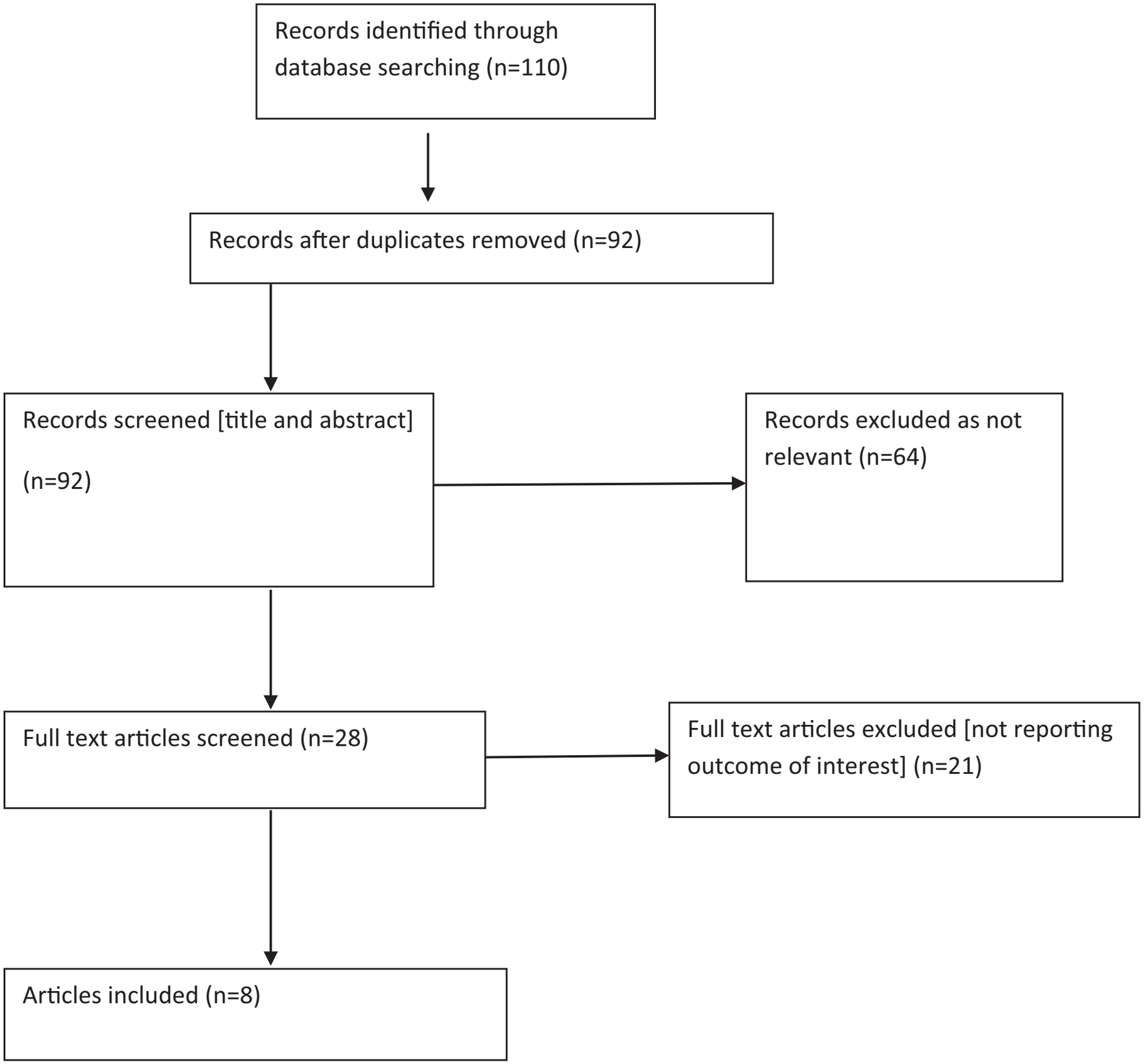
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Figure 1

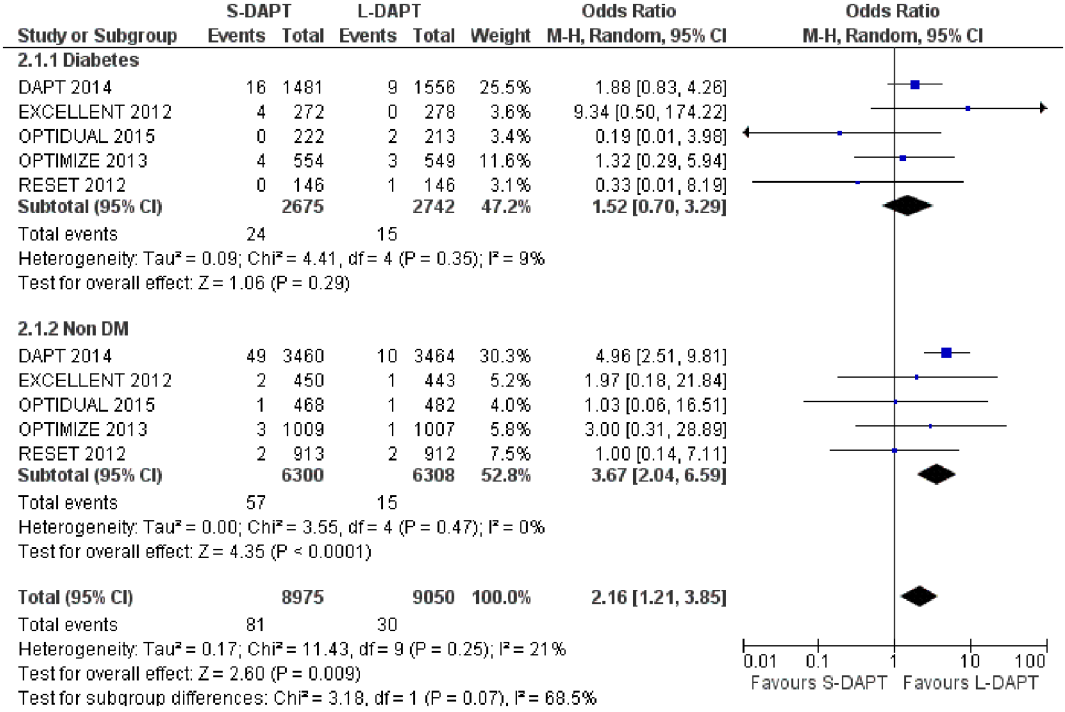
S-DAPT
L-DAPT
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.1.1 Diabetes
DAPT 2014 16 1481 9 1556 25.5% 1.88 [0.83, 4.26]
EXCELLENT 2012 4 272 0 278 3.6% 9.34 [0.50, 174.22]
OPTIDUAL 2015 0 222 2 213 3.4% 0.19 [0.01, 3.98]
OPTIMIZE 2013 4 554 3 549 11.6% 1.32 [0.29, 5.94]
RESET 2012 0 146 1 146 3.1% 0.33 [0.01, 8.19]
Subtotal (95% CI) 2675 2742 47.2% 1.52 [0.70, 3.29]
Total events 24 15
Heterogeneity: Tau² = 0.09; Chi² = 4.41, df = 4 (P = 0.35); I² = 9%
Test for overall effect: Z = 1.06 (P = 0.29)
2.1.2 Non DM
DAPT 2014 49 3460 10 3464 30.3% 4.96 [2.51, 9.81]
EXCELLENT 2012 2 450 1 443 5.2% 1.97 [0.18, 21.84]
OPTIDUAL 2015 1 468 1 482 4.0% 1.03 [0.06, 16.51]
OPTIMIZE 2013 3 1009 1 1007 5.8% 3.00 [0.31, 28.89]
RESET 2012 2 913 2 912 7.5% 1.00 [0.14, 7.11]
Subtotal (95% CI) 6300 6308 52.8% 3.67 [2.04, 6.59]
Total events 57 15
Heterogeneity: Tau² = 0.00; Chi² = 3.55, df = 4 (P = 0.47); I² = 0%
Test for overall effect: Z = 4.35 (P < 0.0001)
Total (95% CI) 8975 9050 100.0% 2.16 [1.21, 3.85]
Total events 81 30
Heterogeneity: Tau² = 0.17; Chi² = 11.43, df = 9 (P = 0.25); I² = 21%
Test for overall effect: Z = 2.60 (P = 0.009)
Test for subgroup differences: Chi² = 3.18, df = 1 (P = 0.07), I² = 68.5%
0.01 0.1 1 10 100
Favours S-DAPT Favours L-DAPT

Figure 2

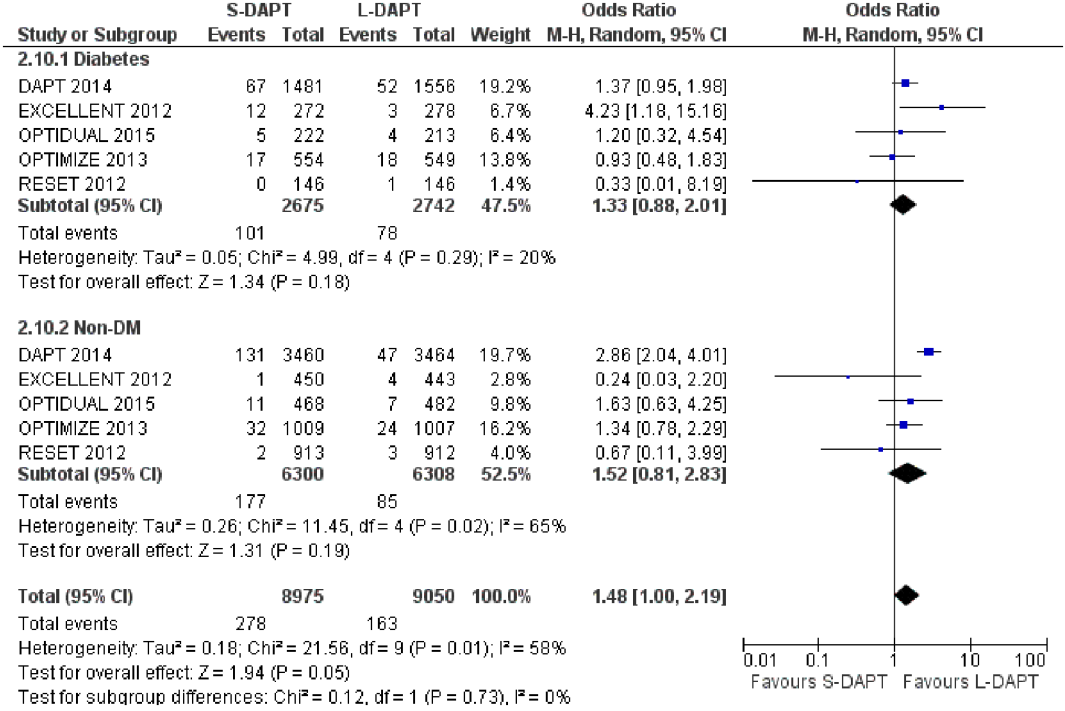
S-DAPT
L-DAPT
Odds Ratio
Odds Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.10.1 Diabetes
DAPT 2014 67 1481 52 1556 19.2% 1.37 [0.95, 1.98]
EXCELLENT 2012 12 272 3 278 6.7% 4.23 [1.18, 15.16]
OPTIDUAL 2015 5 222 4 213 6.4% 1.20 [0.32, 4.54]
OPTIMIZE 2013 17 554 18 549 13.8% 0.93 [0.48, 1.83]
RESET 2012 0 146 1 146 1.4% 0.33 [0.01, 8.19]
Subtotal (95% CI) 2675 2742 47.5% 1.33 [0.88, 2.01]
Total events 101 78
Heterogeneity: Tau² = 0.05; Chi² = 4.99, df = 4 (P = 0.29); I² = 20%
Test for overall effect: Z = 1.34 (P = 0.18)
2.10.2 Non-DM
DAPT 2014 131 3460 47 3464 19.7% 2.86 [2.04, 4.01]
EXCELLENT 2012 1 450 4 443 2.8% 0.24 [0.03, 2.20]
OPTIDUAL 2015 11 468 7 482 9.8% 1.63 [0.63, 4.25]
OPTIMIZE 2013 32 1009 24 1007 16.2% 1.34 [0.78, 2.29]
RESET 2012 2 913 3 912 4.0% 0.67 [0.11, 3.99]
Subtotal (95% CI) 6300 6308 52.5% 1.52 [0.81, 2.83]
Total events 177 85
Heterogeneity: Tau² = 0.26; Chi² = 11.45, df = 4 (P = 0.02); I² = 65%
Test for overall effect: Z = 1.31 (P = 0.19)
Total (95% CI) 8975 9050 100.0% 1.48 [1.00, 2.19]
Total events 278 163
Heterogeneity: Tau² = 0.18; Chi² = 21.56, df = 9 (P = 0.01); I² = 58%
Test for overall effect: Z = 1.94 (P = 0.05)
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%
0.01 0.1 1 10 100
Favours S-DAPT Favours L-DAPT

Figure 3

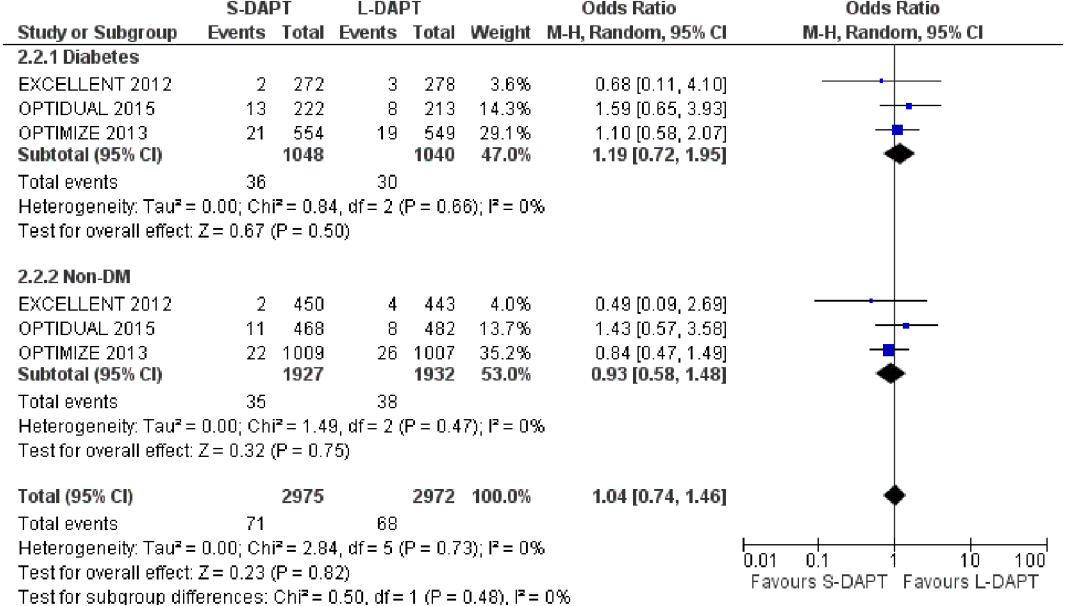
S-DAPT
L-DAPT
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.2.1 Diabetes
EXCELLENT 2012 2 272 3 278 3.6% 0.68 [0.11, 4.10]
OPTIDUAL 2015 13 222 8 213 14.3% 1.59 [0.65, 3.93]
OPTIMIZE 2013 21 554 19 549 29.1% 1.10 [0.58, 2.07]
Subtotal (95% CI) 1048 1040 47.0% 1.19 [0.72, 1.95]
Total events 36 30
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)
2.2.2 Non-DM
EXCELLENT 2012 2 450 4 443 4.0% 0.49 [0.09, 2.69]
OPTIDUAL 2015 11 468 8 482 13.7% 1.43 [0.57, 3.58]
OPTIMIZE 2013 22 1009 26 1007 35.2% 0.84 [0.47, 1.49]
Subtotal (95% CI) 1927 1932 53.0% 0.93 [0.58, 1.48]
Total events 35 38
Heterogeneity: Tau² = 0.00; Chi² = 1.49, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)
Total (95% CI) 2975 2972 100.0% 1.04 [0.74, 1.46]
Total events 71 68
Heterogeneity: Tau² = 0.00; Chi² = 2.84, df = 5 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Chi² = 0.50, df = 1 (P = 0.48), I² = 0%
0.01 0.1 1 10 100
Favours S-DAPT Favours L-DAPT

Figure 4

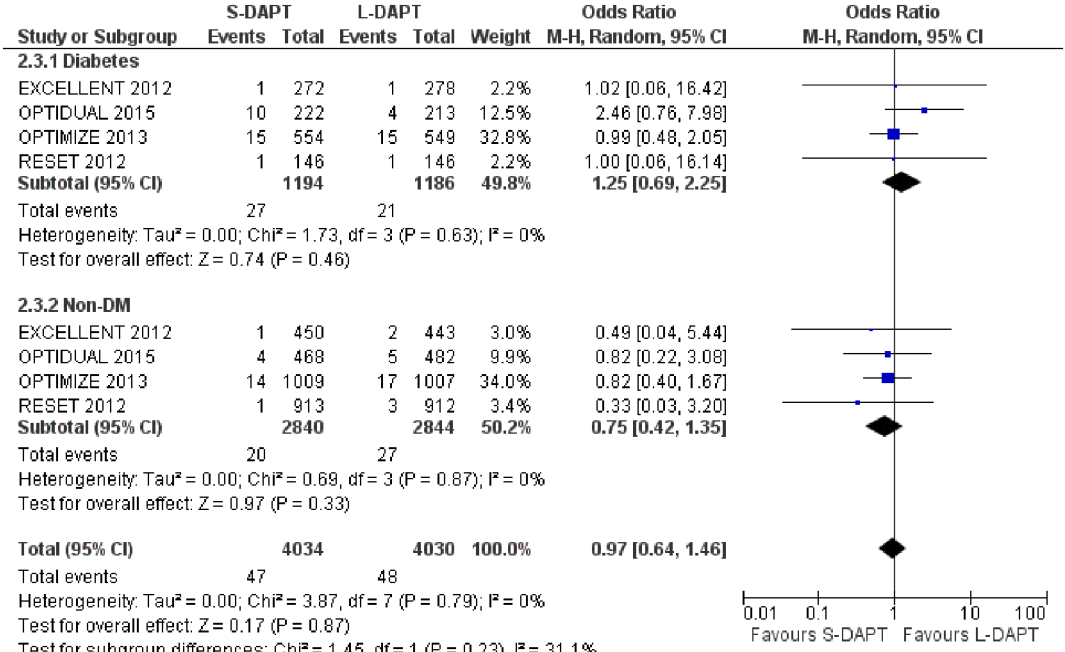
S-DAPT
L-DAPT
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.3.1 Diabetes
EXCELLENT 2012 1 272 1 278 2.2% 1.02 [0.06, 16.42]
OPTIDUAL 2015 10 222 4 213 12.5% 2.46 [0.76, 7.98]
OPTIMIZE 2013 15 554 15 549 32.8% 0.99 [0.48, 2.05]
RESET 2012 1 146 1 146 2.2% 1.00 [0.06, 16.14]
Subtotal (95% CI) 1194 1186 49.8% 1.25 [0.69, 2.25]
Total events 27 21
Heterogeneity: Tau² = 0.00; Chi² = 1.73, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
2.3.2 Non-DM
EXCELLENT 2012 1 450 2 443 3.0% 0.49 [0.04, 5.44]
OPTIDUAL 2015 4 468 5 482 9.9% 0.82 [0.22, 3.08]
OPTIMIZE 2013 14 1009 17 1007 34.0% 0.82 [0.40, 1.67]
RESET 2012 1 913 3 912 3.4% 0.33 [0.03, 3.20]
Subtotal (95% CI) 2840 2844 50.2% 0.75 [0.42, 1.35]
Total events 20 27
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 3 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)
Total (95% CI) 4034 4030 100.0% 0.97 [0.64, 1.46]
Total events 47 48
Heterogeneity: Tau² = 0.00; Chi² = 3.87, df = 7 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.87)
Test for subgroup differences: Chi² = 1.45, df = 1 (P = 0.23), I² = 31.1%
0.01 0.1 1 10 100
Favours S-DAPT Favours L-DAPT

Figure 5

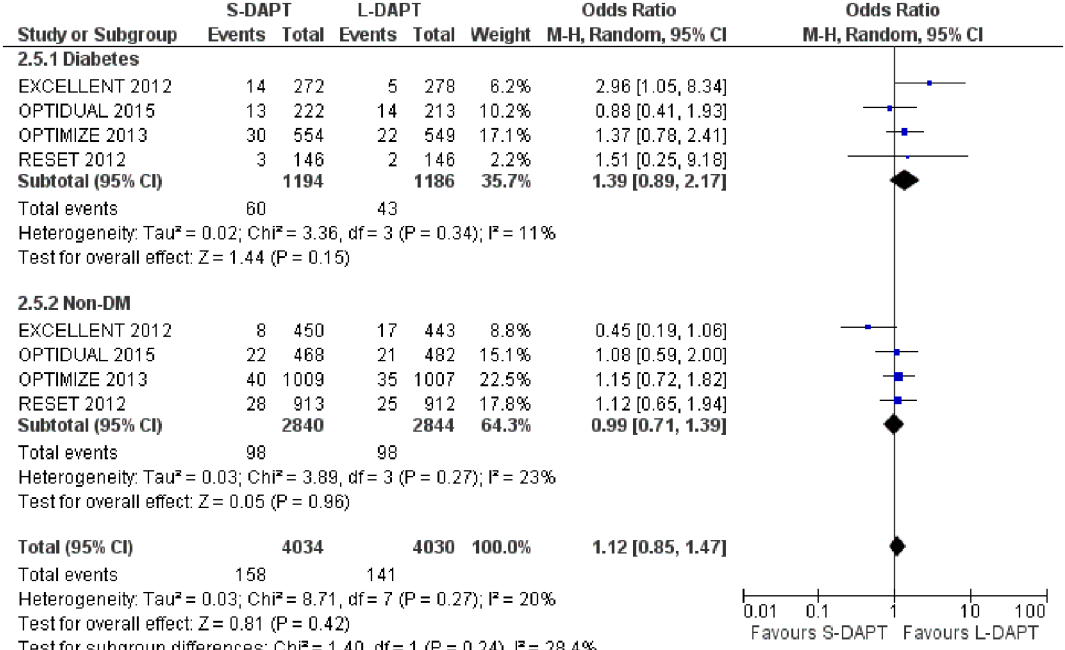
S-DAPT
L-DAPT
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.5.1 Diabetes
EXCELLENT 2012 14 272 5 278 6.2% 2.96 [1.05, 8.34]
OPTIDUAL 2015 13 222 14 213 10.2% 0.88 [0.41, 1.93]
OPTIMIZE 2013 30 554 22 549 17.1% 1.37 [0.78, 2.41]
RESET 2012 3 146 2 146 2.2% 1.51 [0.25, 9.18]
Subtotal (95% CI) 1194 1186 35.7% 1.39 [0.89, 2.17]
Total events 60 43
Heterogeneity: Tau² = 0.02; Chi² = 3.36, df = 3 (P = 0.34); I² = 11%
Test for overall effect: Z = 1.44 (P = 0.15)
2.5.2 Non-DM
EXCELLENT 2012 8 450 17 443 8.8% 0.45 [0.19, 1.06]
OPTIDUAL 2015 22 468 21 482 15.1% 1.08 [0.59, 2.00]
OPTIMIZE 2013 40 1009 35 1007 22.5% 1.15 [0.72, 1.82]
RESET 2012 28 913 25 912 17.8% 1.12 [0.65, 1.94]
Subtotal (95% CI) 2840 2844 64.3% 0.99 [0.71, 1.39]
Total events 98 98
Heterogeneity: Tau² = 0.03; Chi² = 3.89, df = 3 (P = 0.27); I² = 23%
Test for overall effect: Z = 0.05 (P = 0.96)
Total (95% CI) 4034 4030 100.0% 1.12 [0.85, 1.47]
Total events 158 141
Heterogeneity: Tau² = 0.03; Chi² = 8.71, df = 7 (P = 0.27); I² = 20%
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Chi² = 1.40, df = 1 (P = 0.24), I² = 28.4%
0.01 0.1 1 10 100
Favours S-DAPT Favours L-DAPT

Figure 6

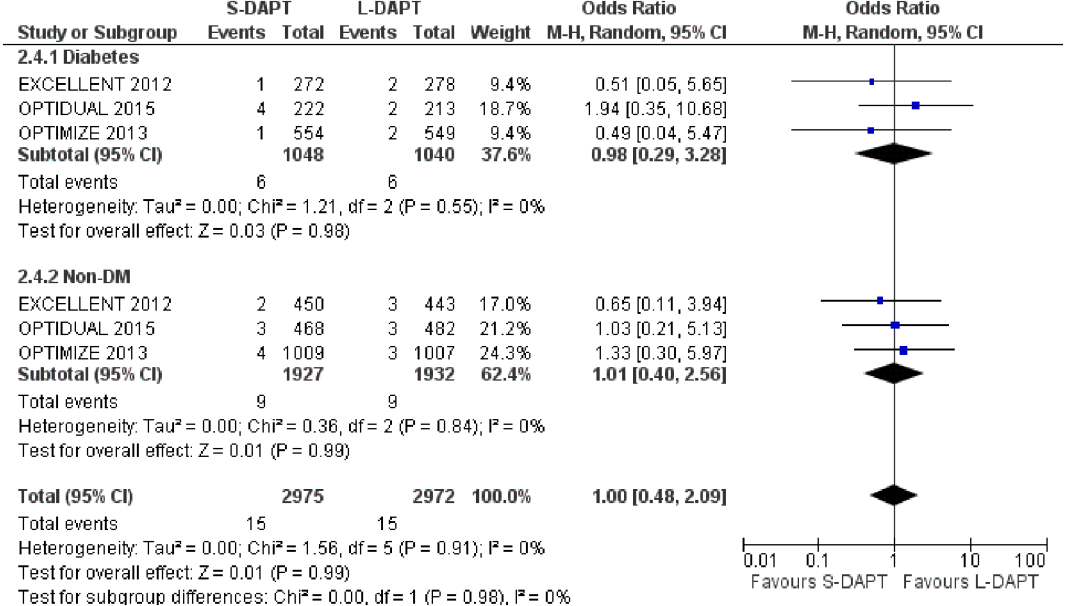
S-DAPT
L-DAPT
Odds Ratio
Odds Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.4.1 Diabetes
EXCELLENT 2012 1 272 2 278 9.4% 0.51 [0.05, 5.65]
OPTIDUAL 2015 4 222 2 213 18.7% 1.94 [0.35, 10.68]
OPTIMIZE 2013 1 554 2 549 9.4% 0.49 [0.04, 5.47]
Subtotal (95% CI) 1048 1040 37.6% 0.98 [0.29, 3.28]
Total events 6 6
Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.98)
2.4.2 Non-DM
EXCELLENT 2012 2 450 3 443 17.0% 0.65 [0.11, 3.94]
OPTIDUAL 2015 3 468 3 482 21.2% 1.03 [0.21, 5.13]
OPTIMIZE 2013 4 1009 3 1007 24.3% 1.33 [0.30, 5.97]
Subtotal (95% CI) 1927 1932 62.4% 1.01 [0.40, 2.56]
Total events 9 9
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 2 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)
Total (95% CI) 2975 2972 100.0% 1.00 [0.48, 2.09]
Total events 15 15
Heterogeneity: Tau² = 0.00; Chi² = 1.56, df = 5 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%
0.01 0.1 1 10 100
Favours S-DAPT Favours L-DAPT

Figure 7

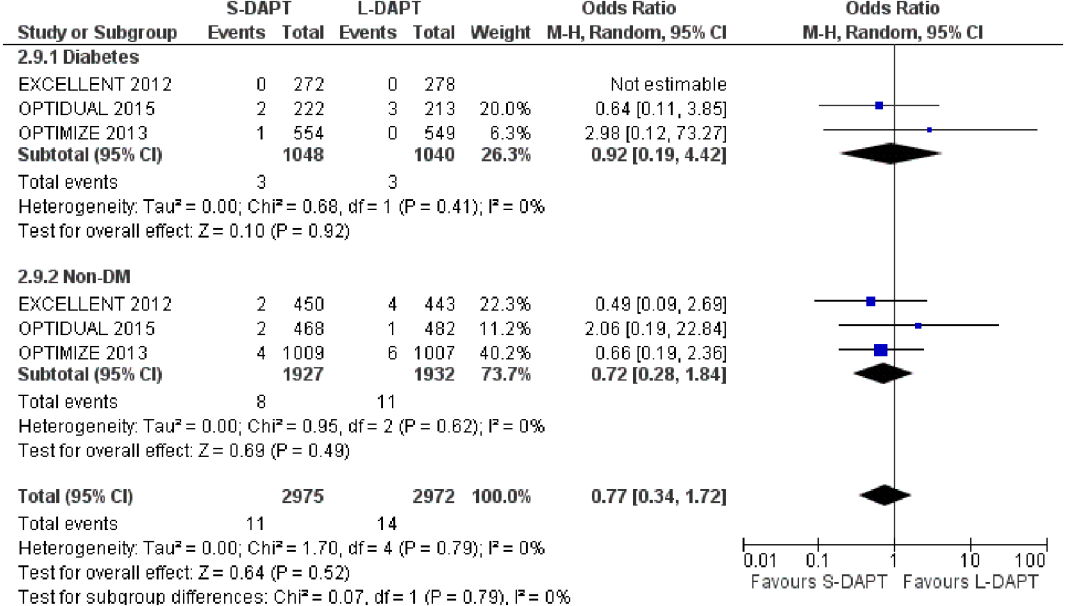
S-DAPT
L-DAPT
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.9.1 Diabetes
EXCELLENT 2012 0 272 0 278 Not estimable
OPTIDUAL 2015 2 222 3 213 20.0% 0.64 [0.11, 3.85]
OPTIMIZE 2013 1 554 0 549 6.3% 2.98 [0.12, 73.27]
Subtotal (95% CI) 1048 1040 26.3% 0.92 [0.19, 4.42]
Total events 3 3
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)
2.9.2 Non-DM
EXCELLENT 2012 2 450 4 443 22.3% 0.49 [0.09, 2.69]
OPTIDUAL 2015 2 468 1 482 11.2% 2.06 [0.19, 22.84]
OPTIMIZE 2013 4 1009 6 1007 40.2% 0.66 [0.19, 2.36]
Subtotal (95% CI) 1927 1932 73.7% 0.72 [0.28, 1.84]
Total events 8 11
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)
Total (95% CI) 2975 2972 100.0% 0.77 [0.34, 1.72]
Total events 11 14
Heterogeneity: Tau² = 0.00; Chi² = 1.70, df = 4 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%
0.01 0.1 1 10 100
Favours S-DAPT Favours L-DAPT

Figure 8

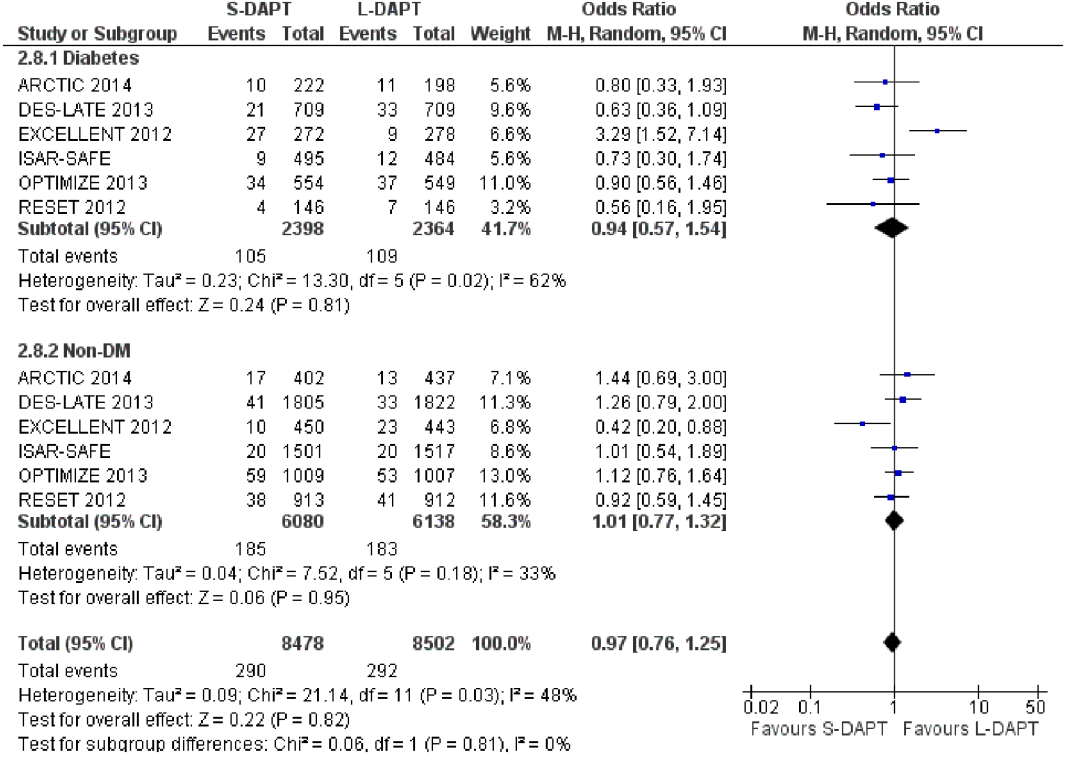
S-DAPT
L-DAPT
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.8.1 Diabetes
ARCTIC 2014 10 222 11 198 5.6% 0.80 [0.33, 1.93]
DES-LATE 2013 21 709 33 709 9.6% 0.63 [0.36, 1.09]
EXCELLENT 2012 27 272 9 278 6.6% 3.29 [1.52, 7.14]
ISAR-SAFE 9 495 12 484 5.6% 0.73 [0.30, 1.74]
OPTIMIZE 2013 34 554 37 549 11.0% 0.90 [0.56, 1.46]
RESET 2012 4 146 7 146 3.2% 0.56 [0.16, 1.95]
Subtotal (95% CI) 2398 2364 41.7% 0.94 [0.57, 1.54]
Total events 105 109
Heterogeneity: Tau² = 0.23; Chi² = 13.30, df = 5 (P = 0.02); I² = 62%
Test for overall effect: Z = 0.24 (P = 0.81)
2.8.2 Non-DM
ARCTIC 2014 17 402 13 437 7.1% 1.44 [0.69, 3.00]
DES-LATE 2013 41 1805 33 1822 11.3% 1.26 [0.79, 2.00]
EXCELLENT 2012 10 450 23 443 6.8% 0.42 [0.20, 0.88]
ISAR-SAFE 20 1501 20 1517 8.6% 1.01 [0.54, 1.89]
OPTIMIZE 2013 59 1009 53 1007 13.0% 1.12 [0.76, 1.64]
RESET 2012 38 913 41 912 11.6% 0.92 [0.59, 1.45]
Subtotal (95% CI) 6080 6138 58.3% 1.01 [0.77, 1.32]
Total events 185 183
Heterogeneity: Tau² = 0.04; Chi² = 7.52, df = 5 (P = 0.18); I² = 33%
Test for overall effect: Z = 0.06 (P = 0.95)
Total (95% CI) 8478 8502 100.0% 0.97 [0.76, 1.25]
Total events 290 292
Heterogeneity: Tau² = 0.09; Chi² = 21.14, df = 11 (P = 0.03); I² = 48%
Test for overall effect: Z = 0.22 (P = 0.82)
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%
0.02 0.1 1 10 50
Favours S-DAPT Favours L-DAPT

Figure 9